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REMARKS

Claims 1-14 are now pending.

The Applicants indeed thank the Examiner for the telephonic communication of March 12, 2008. Per the suggestion of the Examiner a fully-executed rule 132 declaration is accordingly appended hereto to expedite the prosecution of this case.

Summary

The Applicants respectfully highlight to the Examiner that the optically active crystalline calcium salt of fluvastatin and closely related compounds described and claimed herein is not described, suggested or contemplated anywhere in the art prior to the invention.

Fluvastatin, produced and sold commercially as an amorphous sodium salt, continues to exhibit inherent properties that are, *inter alia*, detrimental to commercial production and storage. The current commercial form, for example, is extremely susceptible to degradation at a pH about 8 or below compounded by the high level of hygroscopicity of the amorphous sodium salt.[1] These properties present incessant issues necessarily addressed during manufacture and storage of the current commercial form.

The Applicants have successfully modified these detrimental properties exhibited by the commercial form of fluvastatin after extensive studies and experimentation and ultimately by synthesizing and characterizing a certain optically active crystalline form of a calcium salt of the compound.[2] The Applicants specifically teach in the written description of the present disclosure *specifically* how to manufacture the optically active crystal and ascertain the identity of the exemplary species, *per se*. Needless to say, if the improved form of fluvastatin were obvious at the time of the invention, the longfelt need for improvement of the properties of the commercial product would not exist.

The Supreme Court in KSR recently and unequivocally affirmed the familiar framework for determining obviousness as set forth in Graham v. John Deere Co. (383 U.S. 1, 148 USPQ 459 (1966)). Indeed, the basic approach to determining obviousness remains the same including

[1] See, e.g., Applicant's disclosure at Page 1.

[2] The optically active crystalline calcium salt of fluvastatin described and claimed by the Applicants is, for example, significantly less hygroscopic than the amorphous sodium salt currently in commercial production.

the consideration of evidence of *long-felt but unsolved needs*, the *failure of others*, and *unexpected results*. MPEP E8R6 (September 2007) § 2141.[3] It is axiomatic that a claimed invention is not obvious solely because it is composed of elements that are all individually found in the prior art.[4] Motivation must exist to combine the elements with a reasonable expectation of success at the time of the invention.

35 USC §103:	REFERENCE	DISCLOSURE
•	Kathawala US 5,354,772	Fluvastatin *Sodium* and *Potassium* Salts
•	Van Der Schaaf WO 02/36563	Polymorphs of Fluvastatin *Sodium* Salt
•	Ekwuribe US 6,479,692	Recitation of *Calcium* in laundry list re: Acylanilides

The subject matter of the now pending claims stand rejected as obvious in view of these references.

A. The disclosure of Kathawala is limited to *sodium* and *potassium* salts of fluvastatin and the mere contemplation of "pharmaceutically acceptable cation [salts]".

B. The disclosure of Van Der Schaaf is limited to polymorphs of the current commercial form of the drug, i.e. the *sodium* salt, *per se*.

C. Importantly, the disclosure of Ekwuribe is expressly limited to the synthesis of bicalutamide and related acylanilides (antiandrogens for the treatment of prostate cancer). Pharmaceutically acceptable salts of the acylanilides are contemplated generically in a laundry list, i.e.,

> "Acylanilides **synthesized by the methods disclosed herein** can be prepared in the form of **their** pharmaceutically acceptable salts. Examples of such salts are (a) acid addition salts formed with inorganic acids, for example hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, nitric acid and the like; and salts formed with organic acids such as, for example, acetic acid, oxalic acid, lactic acid, tartaric acid, succinic acid, malic acid, ascorbic acid, benzoic acid, methanesulfonic acid, p-toluenesulfonic acid,

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[3] KSR Int'l Co. v. Teleflex Inc., 550 U.S. —, 82 USPQ2d 1385 (2007).

naphthalenedisulfonic acid, polygalacturonic acid, and the like; (b) salts formed from elemental anions such as chlorine, bromine, and iodine, and (c) salts derived from bases, such as ammonium salts, alkali metal salts such as those of sodium and potassium, alkaline earth metal salts such as those of **calcium** and magnesium, and salts with organic bases such as dicyclohexylamine and N-methyl-D-glucamine."

Emphasis added. Col.11, lines 13-31.

The language of the claims now pending, however, do not encompass acylanilides (antiandrogens for the treatment of prostate cancer). In sharp contrast, the subject matter of the present invention is drawn toward entirely distinct chemical structural genera which exhibit an entirely diverse and distinct function in an entirely diverse and distinct area of therapeutic intervention, i.e., inhibitors of 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA) reductase for the treatment of hypercholesteremia.

The Applicants respectfully highlight to the Examiner that Nowhere in the disclosures of either Kathawala or Van Der Schaaf are calcium salts of fluvastatin or related compounds described, suggested or contemplated. Only in the laundry list of Ekwuribe, reproduced *supra*, is calcium even remotely contemplated as a cation for *acylanilides*.

1. The Applicants respectfully submit that the cited references even when combined do not suggest the employment of calcium as a cation for fluvastatin and related compounds to one of ordinary skill in the art at the time of the invention with a reasonable expectation of success.

2. The Applicants teach, and the claims are so limited, to specifically how to make optically active crystalline *calcium* salts of fluvastatin *and closely related compounds*.

The subject matter of claim 8, for example, is limited to an optically active crystalline calcium salt of fluvastatin which exhibits a powder X-ray diffraction pattern with maxima at 2θ values of 5.3, 11.8, 13.9, 17.5, 19.1, 22.0 and 23.1 and which has a melting point of about 220°C. See, e.g., Applicant's disclosure at Page 5.

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[4] Importantly, the Supreme Court reaffirmed that"[t]he combination of familiar elements according to known methods is likely to be obvious when it does no more than yield *predictable* results." Emphasis added. Id. at ___, 82 USPQ2d at 1395.

Since none o the claims now pending encompass anything contemplated within the disclosures of Katha vala, Van Der Schaaf, and/or Ekwuribe the subject matter within the proper scope of claim now pending cannot be obvious as a matter of law. The Applicants moreover illustrate an otherwise unexpected decreased hygroscopicity of the calcium salt in relation to the sodium salt of the same compound (presented in a Rule 132 Declaration submitted herewith). The calcium salt of fluvastatin is considerably less hygroscopic than the sodium salt, i.e., 2.8% gain at 84% relative humidity (RH) vs. 26.0% gain at 84% RH, respectively. The Applicants respectfully request the Examiner to withdraw all rejections under 35 USC § 103.

The Applicants respectfully submit that claims 1-14 are in condition for allowance. Early action toward this end is courteously solicited. The Examiner is kindly encouraged to telephone the undersigned in order to expedite any detail of the prosecution. The Commissioner is authorized to charge any deficiency or credit any overpayment to Deposit Account No. 02-2556.

Respectfully submitted,

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